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Photoredox-Mediated Synthesis of Functionalized Sulfoxides from Terminal Alkynes

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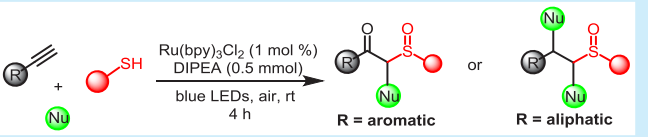
ABSTRACT: A photoredox-mediated protocol for the synthesis of α-alkoxy-β-ketosulfoxides and α,β-dialkoxysulfoxides using alkynes, thiol, and alcohols is reported. This work presents a rare single-step synthesis of α-substituted sulfoxides, involving tandem introduction of a thiol and alcohol as a key enabling advancement. Furthermore, the method can be easily employed to access vinyl sulfoxides and β-ketosulfoxides.



Sulfoxides are valuable synthetic intermediates and a key structural building block of a large number of naturally occurring and pharmacologically active molecules such as sulindac, mesoridazine, and sulfinpyrazone.[1] Notably, sulfur is the third most found heteroatom in FDA-approved drugs and comprises one-fifth of the 200 most prescribed pharmaceutical products.[2] Conventionally, the synthesis of sulfoxides relies on the oxidation of sulfides using strong/toxic oxidizing agents in stoichiometric or excess amounts with associated side products resulting from over or under oxidation.[3] Furthermore, this becomes even more challenging in cases where we may wish to synthesize α-substituted sulfoxides, as their direct synthesis has remained elusive so far. The only approach to access α-substituted sulfoxides besides oxidation of sulfides involves generation of an α-sulfinyl carbanion using a strong base for attack on electrophilic centers, limiting them to α-alkyl substitution.[4] Despite these advances, and possibly due to low bond dissociation energies of the C−S bond,[5] the synthesis of α-alkoxysulfoxides is hitherto unreported. Besides, most of the work in the past has been around Pummerer rearrangement, which is limited to the synthesis of α-substituted sulfides (Figure 1).[6] Moreover, the Pummerer rearrangement requires multiple steps as alkyl sulfoxide is typically its substrate, which requires further dehydration to create a thionium ion for the addition of nucleophiles. In this regard, previous reports[7] including that from our group[8] have shown vinyl radicals emanating from radical additions where thiyl radicals on alkynes can be utilized for diverse functionalizations. Herein, we report a direct approach toward the synthesis of α-alkoxy-β-ketosulfoxides and α,β-dialkoxysulfoxides via photoredox catalysis involving tandem diastereoselective introduction of two nucleophile, viz., alcohol and thiol. The work is also significant from the perspective that geminal difunctionalization of ketones is itself a challenging task, as introduction of a second group requires a sequential deprotonation for further enolization.[9]

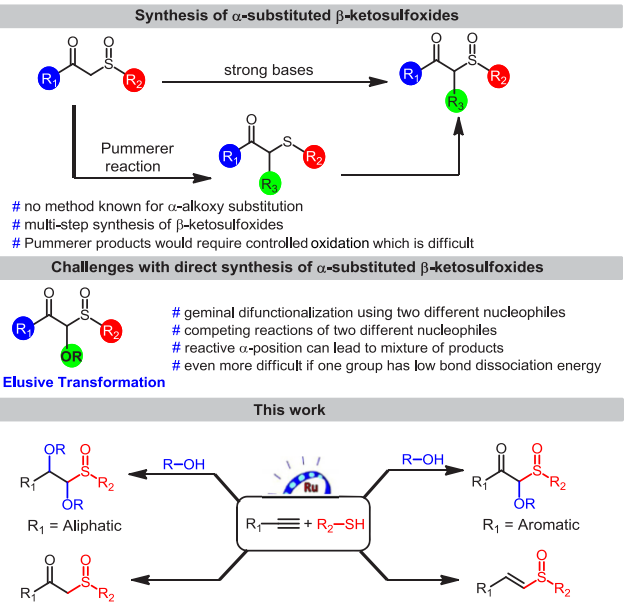


Figure 1. Synthesis of substituted sulfoxides.

Furthermore, the reaction could be easily extended for the synthesis of β-ketosulfoxides and vinyl sulfoxides in the absence of a nucleophile, which as it turns out are substrates for Pummerer reaction and in principle can be applied to access a plethora of functionalized scaffolds.[14b]

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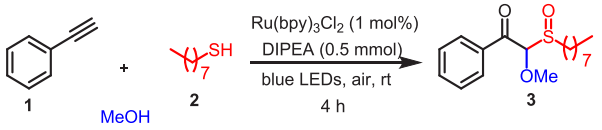
Our efforts commenced with the reaction of phenylacetylene (**1**) and 1-octanethiol (**2**) in the presence of $Ru(bpy)_3Cl_2$ as a photocatalyst and DIPEA as a base (Table 1, entry 1). The

Table 1. Optimization of Reaction Conditions[a]



entry	deviation from standard conditions	yield (%) of 3[a]
1	none	70
2	pyridine instead of DIPEA	31
3	Et_3N instead of DIPEA	53
4	NaOMe instead of DIPEA	39
5	Cs_2CO_3 instead of DIPEA	traces
6	Mes-$Acr^+ClO_4^-$ as photocatalyst	44
7	eosin-Y as photocatalyst	traces
8	Rose Bengal as photocatalyst	38
9	no photocatalyst, light, or base	n.d.

[a]Reaction conditions: phenylacetylene (**1**, 1 mmol), 1-octanethiol (**2**, 1.5 mmol), photocatalyst (1 mol %), base (0.5 mmol), MeOH (1 mL), irradiation under air atmosphere, blue LEDs, room temperature: 25 °C, time: 4 h.

irradiation of the reaction mixture under blue LEDs in MeOH as solvent led to the formation of α-methoxy-β-ketosulfoxide (**3**) in 70% yield. To study the behavior of the reaction, various bases as well as photocatalysts were also screened. The reaction in the presence of pyridine, Et_3N, NaOMe, and CS_2CO_3 did not improve the yields (Table 1, entries 2−5). The use of Mes-$Acr^+ClO_4^-$ gave the corresponding sulfoxide in 44% yield (Table 1, entry 6), whereas trace amounts of product were observed in the presence of eosin-Y and Rose Bengal (Table 1, entries 7 and 8). Furthermore, control experiments established the importance of photocatalyst, light source, and base, as negligible or no product formation was observed in the absence of these entities (Table 1, entry 9).

Having conditions optimized, we then proceeded for the evaluation of substrate scope of the reaction with a range of alkynes, thiols, and alcohols (Scheme 1). A wide range of phenylacetylenes served as suitable coupling partners with 1-octanethiol. The reaction with various halo-substituted phenylacetylenes like 4-fluoro, 3-chloro, 4-bromo, and 3,5-difluoro gave corresponding α-methoxy-β-ketosulfoxides **4**−**7** in 53−62% yields. The electron-deficient 4-trifluoromethyl-substituted phenylacetylene also reacted to produce compound **8** in 51% yield. The electron-rich phenylacetylenes bearing 4-ethyl, 4-propyl, 4-pentyl, 4-*tert*-butyl, and 4-methoxy substituents participated efficiently in this three-component reaction to generate the corresponding sulfoxides **9**−**13** in 54−61% yields. In addition, various aliphatic thiols like 1-hexanethiol, 1-pentanethiol, and 1-butanethiol showed good reactivity to yield products **14**−**16** in 66−70% yields. A range of thiophenols bearing functional groups like 4-methoxy, 2,5-dimethyl, and 3-Br thiophenol generated the corresponding products **17**−**19** in good yields.

Encouraged by these transformations, we became intrigued to explore the feasibility of the reaction with other alcohols. To our delight, replacement of methanol as a solvent by ethanol resulted in the formation of the ethoxy-substituted product **20** in 58% yield. Even isopropanol, trifluoroethanol, methanol-d_4, phenol, and benzyl alcohol proved to be competent nucleophiles to afford products **21**−**25** in good yields. Furthermore, acetic anhydride and propionic anhydride also proved unproblematic under standardized reaction conditions to give corresponding products **26** and **27** in good yields. The above results reflect the broader applicability of this method in terms of introducing different nucleophiles in the ketosulfoxide framework. Next, we sought to examine the behavior of this reaction with different aliphatic acetylenes. To our surprise, the reaction of thiophenol with 1-octyne instead led to the formation of α,β-dimethoxysulfoxide (**28**) in 64% yields. This can possibly be explained based on the lower stability of the vinyl radical in the case of aliphatic acetylenes rendering them more reactive toward the thiol. The reaction was also feasible with 1-heptyne and cyclopropyl acetylene to give corresponding dimethoxy derivatives **29** and **30** in good yields. The transformation was also expandable to various thiophenols like 4-tolyl, 4-F, 4-Cl, 4-Br, 4-ethyl, and 4-*tert*-butyl thiophenol to yield corresponding sulfoxides **31**−**36** in 52−68% yields.

To gain mechanistic insights and further broaden the substrate scope, we explored the reaction outcome in acetonitrile. The reaction of phenylacetylene and thiophenol pleasingly led to the synthesis of β-ketosulfoxide (**37**) in 67% yields. To the best of our knowledge, this is first report for the synthesis of β-ketosulfoxides from phenylacetylenes. Notably, β-ketosulfoxides find extensive applications in the pharmaceutical industry and synthetic organic chemistry as auxiliaries or precursors for asymmetric synthesis.[10,1a] To establish the generality and scope of this transformation, we carried out this reaction with a range of alkynes and thiols. The reaction of thiophenol proceeded smoothly with different halo-substituted 4-F, 3-Cl, and 3,5-difluoro phenylacetylenes to give corresponding β-ketosulfoxides **38**−**40** in 65−68% yields. Likewise, 4-methyl, 4-propyl, 4-pentyl, 2,4,5-trimethyl, 4-*tert*-butyl, 4-methoxy, and 4-CF_3 phenylacetylene reacted efficiently with thiophenol to generate corresponding sulfoxides **41**−**47** in good yields. Furthermore, aliphatic acetylenes such as 1-pentyne, 1-hexyne, 1-octyne, and 1-nonyne were also suitable reactants, giving the desired products **48**−**51** in 54−61% yields. Next, we screened different thiols for the synthesis of β-ketosulfoxides. The phenylacetylene appeared as a suitable reactant for the reaction with a variety of thiols such as 2-F, 2-Br, 2,6-dichloro, 3-methyl, 4-methyl, 2,5-dimethyl, 4-ethyl, 3-methoxy, and 4-*tert*-butyl thiophenol to yield the corresponding products **52**−**60** in good yields. Aliphatic thiols like 1-pentanethiol and 1-octanethiol also participated in the reaction to produce the corresponding sulfoxides **61**−**62** in 56−58% yields.

Next, we sought to study the fate of reaction in water. We were pleased to see that the reaction of phenylacetylene and thiophenol in water led to the formation of vinyl sulfoxide **63** in 52% yield (Scheme 2). 1-Hexyne and cyclopropyl acetylene were also used for the synthesis of vinyl sulfoxides **64**−**65** in 51 and 55% yields, respectively. Moreover, phenylacetylene as well as various substituted phenylacetylenes such as 4-pentyl, 4-*tert*-butyl, 4-propyl, and 4-methoxy phenylacetylene reacted efficiently with 1-octanethiol to give a range of vinyl sulfoxides **66**−**70** in good yields.

In order to gain further insights into the mechanism, additional experiments were carried out. As depicted when TEMPO was used as a radical scavenger under standard reaction conditions, the reaction was completely inhibited. The use of benzoquinone as a scavenger of superoxide radical also resulted in almost complete inhibition of the reaction.[11]

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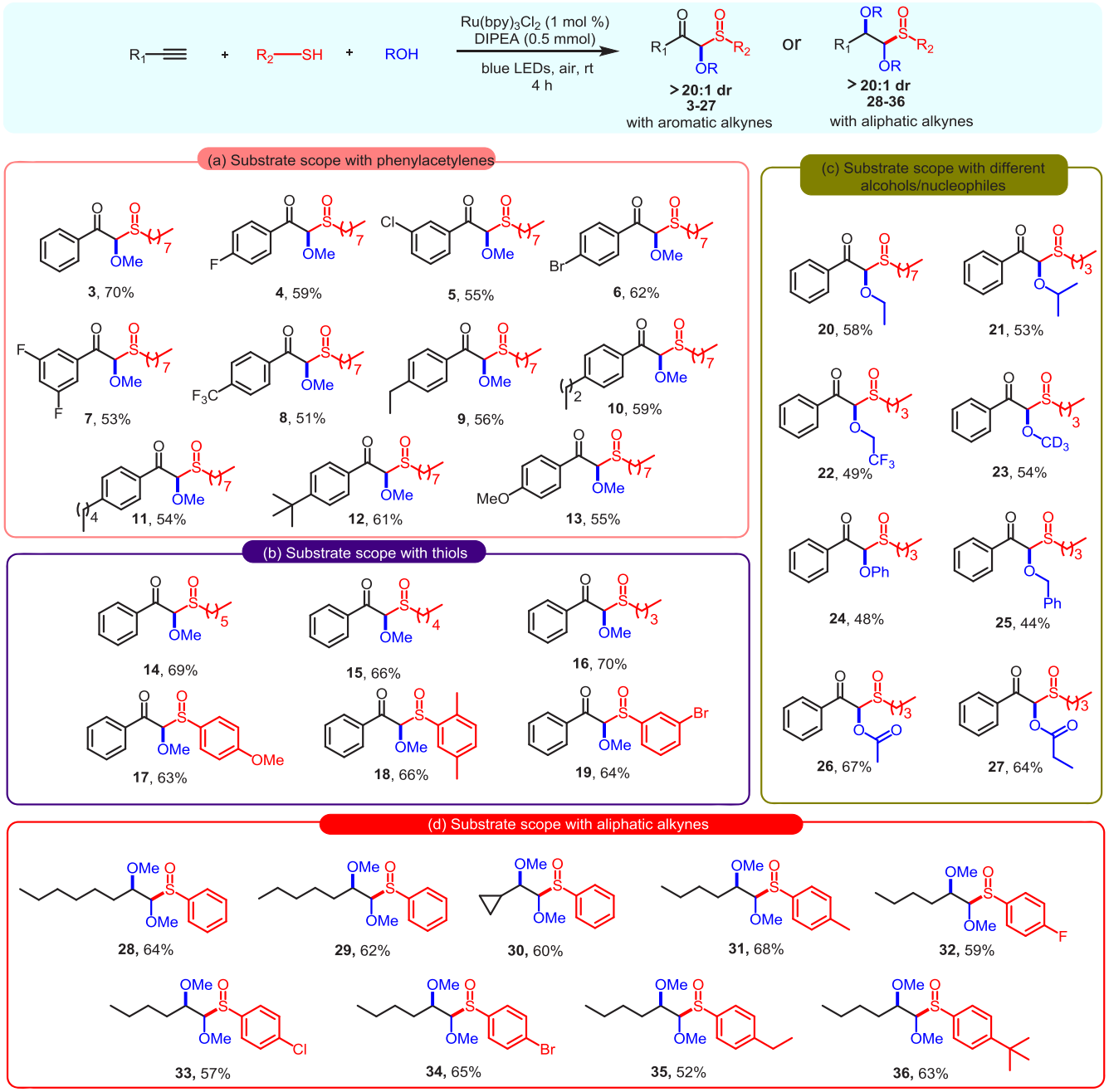
Scheme 1. Substrate Scope for the Synthesis of α-Alkoxy-β-ketosulfoxides and α,β-Dimethoxysulfoxides[a]



[a]Note: (i) alkyne (1 mmol), thiol (1.5 mmol), alcohol: as a solvent. (ii) Reaction of phenol was carried out in water.

Furthermore, we could observe product in trace amounts only under an argon (degassed) atmosphere or in the absence of light or without catalyst. The ^{18}O-labeling experiment with isotope-labeled water ($H_2{}^{18}O$) was performed to determine the source of oxygen in sulfoxide (see Supporting Information). The results show that the oxygen is sourced from air in the reaction.[8a,17a] The photoluminescence quenching studies of the $[Ru(bpy)_3]Cl_2$ photocatalyst with all the reaction ingredients were analyzed using the Stern−Volmer model. Among the various possible quenchers in the reaction system, the photoluminescence of $[Ru(bpy)_3]Cl_2$ was efficiently quenched by thiophenol in methanol solvent, supporting the proposed thiyl radical path as a probable SET mechanism (see Supporting Information). Based on control experiments and literature precedence, a plausible reaction mechanism is depicted in Scheme 3.

The photoexcited $[Ru]^{2+}$* generated from $[Ru]^{2+}$ under blue LEDs irradiation undergoes reductive quenching with thiophenol to give a thiyl radical cation that deprotonates in the presence of a peroxy radical anion to give thiyl radical **I**.[12] The $[Ru]^{2+}$ is regenerated by molecular oxygen.[13] This is followed by the addition of a thiyl radical to the alkyne **1** to give vinyl radical adduct **II**,[14] which can possibly follow two different paths. For the formation of α-methoxy-β-ketosulfoxides, the vinyl radical on hydroperoxide insertion gives peroxy intermediate **III**, which on subsequent peroxide cleavage[15] produces β-ketosulfide **V**. An electron transfer between the photoexcited $[Ru]^{2+}$* generates radical cation **VI**,

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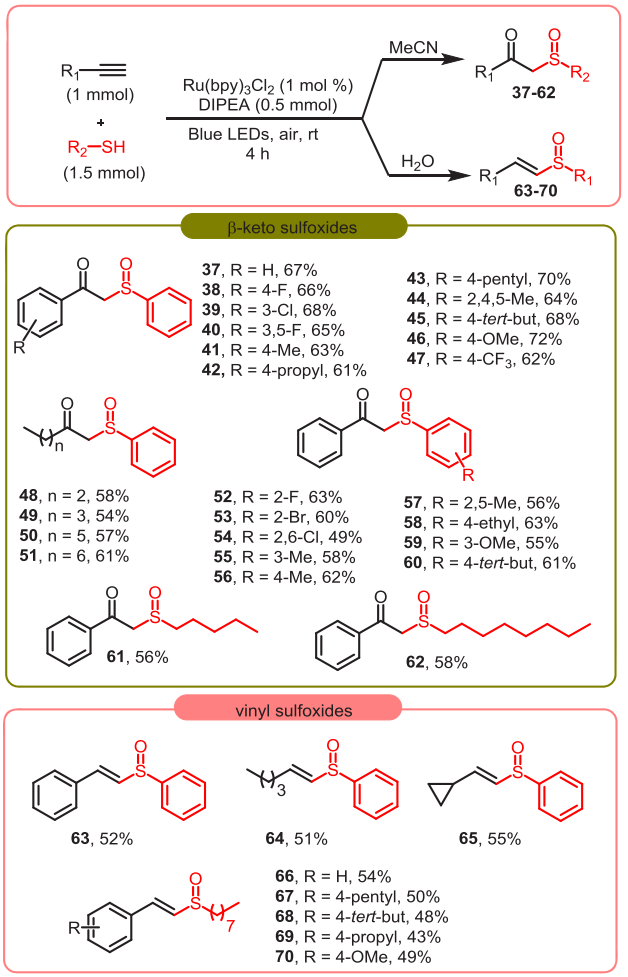
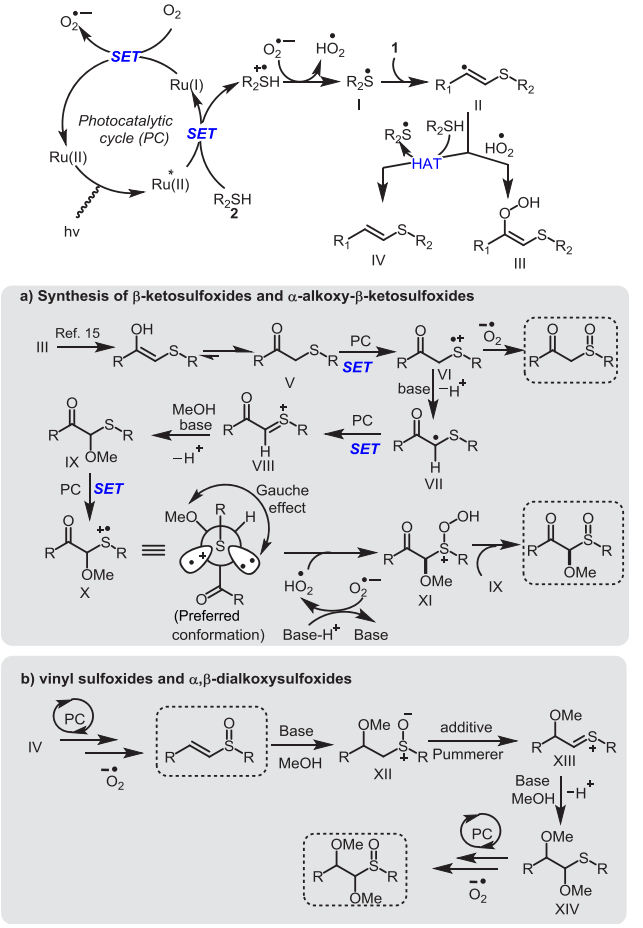
Scheme 2. Substrate Scope for the Synthesis of β-Ketosulfoxides and Vinylsulfoxides



Scheme 3. Plausible Mechanism



which on loss of a proton in the presence of base gives radical intermediate **VII**. The radical intermediate **VII** is available for another electron transfer with $[Ru]^{2+*}$ to give thionium intermediate **VIII**, which on nucleophilic attack at the α-position produces α-methoxy-β-ketosulfide intermediate **IX**. The intermediate **IX** in the presence of $[Ru]^{2+*}$ gives radical cation **X**,[16] which reacts with the oxygen radical anion to produce persulfoxide intermediate **XI**. The intermediate **XI** consequently delivers the α-methoxy-β-ketosulfoxide with another sulfide **IX**.[17] The base-H (DIPEA) in the reaction is possibly regenerated while donating its proton to persulfoxide intermediate **XI**. The intermediate **VI** in the absence of nucleophiles undergoes sensitized photooxidation with dioxygen, producing β-ketosulfoxide. In the case of aliphatic alkynes, we believe due to less stability of the vinyl radical that a hydrogen atom transfer (HAT) between the vinyl radical and thiol is more favored to produce vinyl sulfide and a thiyl radical.[18] The vinyl sulfide **IV** on photooxidation with dioxygen leads to the formation of alkenylsulfoxides. The alkenyl sulfoxides can undergo Pummerer reaction[19] in the presence of a nucleophile at α and β positions to give α,β-dimethoxy sulfide **XIV** which on photooxidation with dioxygen gives α,β-dimethoxysulfoxides. The diastereoselective formation of α-methoxy-β-ketosulfoxide may be attributed to Gauche effects.[20a] Out of various possible conformations of the α-methoxy-β-ketosulfide radical cation (**X**), the one in which a lone pair is antiperiplanar to the heteroatom is preferred because of the stabilizing interaction (hyperconjugation) between the unshared electron pair and the σ*-orbital of the C−O bond. Notably, in the case of α,β-dimethoxysulfoxides the predominant isomer is possibly anti, as there is a sufficient upfield shift of the β-carbon. This can be because of the γ-gauche effect, according to which the upfield shift is only observed for that γ-gauche position, in which the respective β-carbon is anti to the sulfoxides-sulfur lone pair, while the carbons which are synclinal to sulfoxide lone pair are not affected.[20b]

In summary, a new photocatalytic strategy to introduce diverse alkoxide functionalities into the α- and β-position of sulfoxides using $Ru(bpy)_3Cl_2$ as a photocatalyst has been developed. The protocol presents a remarkable tandem introduction of two nucleophiles, viz., alcohol and thiol, as a key to enabling advancement. Moreover, it uses atmospheric oxygen for the oxidation of sulfides to sulfoxides, thereby circumventing the requirement of any external oxidizing agents. Further development of related radical reactions, including catalytic versions mediated by photocatalysts, is currently under investigation in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02055.

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Experimental procedures, characterization data, and ^{1}H and ^{13}C NMR spectra of all compounds (PDF)

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Author Contributions

‖J.K. and A.A. contributed equally to this work.

Notes

The authors declare no competing financial interest.

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